Statement of

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before

the Senate Appropriations Subcommittee on Labor, Health and Human Services, Education and Related Agencies

December 2, 1998

Mr. Chairman and Members of the Subcommittee, I am Harold Varmus, Director of the National Institutes of Health. I am pleased to appear before you to discuss recent published reports on the isolation and propagation of the first human pluripotent stem cell lines. These findings, reported by Drs. John Gearhart from Johns Hopkins University and James Thomson from the University of Wisconsin, bring medical research to the edge of a new frontier that is extraordinarily promising. The development of human pluripotent stem cell lines deserves close scientific examination, further evaluation of the promise of the research, and careful consideration and open discussion of the ethical and legal issues. I want to thank you for the opportunity to discuss this important issue with you and the Members of this Subcommittee.

Why the excitement? For the first time, scientists have obtained human stem cells that can give rise to many types of cells in our body. Let me briefly describe these experiments. Dr. Thomson and coworkers derived stem cell lines from embryos donated by couples undergoing in vitro fertilization (IVF) as part of treatment for infertility. These cells were grown in culture and found to divide indefinitely and have the ability to form cells of the three major tissue types–endoderm (which goes on to form the lining of the gut), mesoderm (which gives rise to muscle, bone and blood) and ectoderm (which gives rise to epidermal tissues and the nervous system). The ability of the cells to specialize into the three major tissues types is an important indicator that these cells are pluripotent. Dr. Gearhart and his coworkers derived pluripotent stem cells from fetal gonadal tissue destined to form germ cells. When grown in culture, these cells resemble other types of pluripotent stem cells in that they, like the cells from Dr. Thomson's work, also can develop into cells of the three major tissue types.

What Are Stem Cells?

As policy makers proceed to consider the scientific, ethical and societal issues raised by this research, it is absolutely essential to clarify terms and definitions. There are many types of stem cells. In general, they all have the ability to divide (and self renew) and to commit to a more

specialized function. There is a hierarchy of stem cell types. Some stem cells are more committed than others. Some stems cells - the pluripotent stem cell we are discussing today - have the ability to become many, but not all, of the cells types in the human body.

Through processes we are only beginning to understand, primitive stem cells can be stimulated to become specialized, so that they are precursors to any one of many different cell types such as muscle cells, skin cells, nerve cells, liver cells. Unlike the stem cells from which they are derived, these specialized cells are "committed" to a particular function.

All stem cells have the capability of self-renewal, i.e., they can continually reproduce themselves. Cells from the very earliest embryo (up to about the 16 cell stage) are totipotent stem cells. They are "totally potent" or totally capable of forming all cells of the body, including the cells required to support embryonic and fetal development. Each cell of this early embryo has the potential to develop into a human being.

After a few days of development, the early embryo forms a hollow ball of cells, called a blastocyst. This is the next stage of embryonic development. The clustered cells within this ball are called the inner cell mass. The cells in the inner cell mass are not totipotent. Rather, they are pluripotent. Pluripotent stem cells are more "committed" than totipotent stem cells. Unlike the fertilized egg, or the early embryo, or the intact blastocyst, neither the disaggregated inner cell mass nor the pluripotent stem cells derived from it (nor the pluripotent stem cells derived from fetal germ cells) will produce a human being even if returned to a woman's uterus. These cells do not have the potential to form a human being, because they do not have the capacity to give rise to the cells of the placenta or other extraembryonic tissues necessary for implantation, nor can they support fetal development in the uterus.

During fetal development, pluripotent stem cells become even more committed, i.e, they have the capacity to form only one or a few different kinds of cells. For example, hematopoietic stem cells can form all the blood cells, but no other tissue types. The adult human being continues to harbor

many types of stem cells responsible for the body's ability to repair some but not all tissues. Stem cells that permit new skin growth and renewal of blood cells are two examples.

Potential Applications of Pluripotent Stem Cells

There are several important reasons why the isolation of human pluripotent stem cells is, indeed, important to science and for the future of public health. At the most fundamental level, pluripotent stem cells could help us to understand the complex events that occur during human development. A primary goal of this work would be the most basic kind of research -- the identification of the factors involved in the cellular decision-making process that determines cell specialization. We know that turning genes on and off is central to this process, but we do not know much about these "decision-making" genes or what turns them on or off. Some of our most serious diseases, like cancer, are due to abnormal cell differentiation and growth. A deeper understanding of normal cell processes will allow us to further delineate the fundamental errors that cause these deadly illnesses.

Human pluripotent stem cell research could also dramatically change the way we develop drugs and test them for safety and efficacy. Rather than evaluating safety and efficacy of a candidate drug in an animal model of a human disease, these drugs could be tested against a human cell line that had been developed to mimic the disease processes. This would not replace whole animal and human testing, but it would streamline the road to discovery. Only the most effective and safest candidate would be likely to graduate to whole animal and then human testing.

Perhaps the most far-reaching potential application of human pluripotent stem cells is the generation of cells and tissue that could be used for transplantation, so-called cell therapies. Many diseases and disorders result from disruption of cellular function or destruction of tissues of the body. Today, donated organs and tissues are often used to replace the function of ailing or destroyed tissue. Unfortunately, the number of people suffering from these disorders far outstrips

the number of organs available for transplantation. Pluripotent stem cells stimulated to develop into specialized cells offer the possibility of a renewable source of replacement cells and tissue to treat a myriad of diseases, conditions and disabilities including Parkinson's and Alzheimer's disease, spinal cord injury, stroke, burns, heart disease, diabetes, osteoarthritis and rheumatoid arthritis. There is almost no realm of medicine that might not be touched by this innovation. Let me expand on two of these examples.

- Transplant of healthy heart muscle cells could provide new hope for heart attack victims. The hope is to develop heart muscle cells from human pluripotent stem cells and transplant them into the failing heart muscle in order to augment the function of the heart. Preliminary work in mice and other animals has demonstrated that healthy heart muscle cells transplanted into the heart successfully repopulate the heart tissue and integrate with the host cells. These experiments show that this type of transplantation is feasible.

- In the many individuals who suffer from Type I diabetes, the production of insulin by the pancreas by specialized cells called islet cells is disrupted. There is evidence that transplantation of either the entire pancreas or isolated islet cells could mitigate the need for insulin injections. Islet cell lines derived from human pluripotent stem cells could be used for this critical research and, ultimately, for transplantation.

While I have taken this opportunity to outline the promise of this research, there is much to be done before we can realize these innovations. First, we must do the basic research to understand the cellular events that lead to cell specialization in the human, so that we can direct these pluripotent stem cells to become the type(s) of tissue needed for transplantation in great numbers. And before we can use these cells for transplantation, we must overcome the well-known problem of immune rejection. Because human pluripotent stem cells derived from embryos or fetal tissue would likely be genetically different from the recipient, future research would need to focus on modifying human pluripotent stem cells to minimize tissue incompatibility. Technological

challenges remain before these discoveries can be incorporated into clinical practice. These challenges, though significant, are not insurmountable.

How Are Pluripotent Stem Cells Produced?

There are several ways to produce human pluripotent stem cells. These methods have been developed over the past 17 years by researchers working with animals. The work you will hear about today builds on this important basic animal research.

As I mentioned earlier, one method of creating these pluripotent stem cells was described by Dr. Thomson and his coworkers. The techniques they used were initially developed using mice. Dr. Thomson first made stem cells from non-human primates. In the most recent work, they used inner cell mass cells from blastocyst stage human embryos that were created in the course of infertility treatment and donated by couples for research to derive stem cells. The researchers allowed cell division to continue in culture to the blastocyst stage and then removed the inner cell mass, which was cultured to derive pluripotent stem cells.

Pluripotent stem cells can also be derived from fetal tissue, as was first done using primordial germ cells from mouse fetal tissue. Dr. Gearhart and coworkers isolated human primordial germ cells, the cells that will go on to become eggs and sperm, from 5-9 week old fetal tissue obtained after pregnancy termination. When grown in culture, these stem cells appear to be pluripotent.

It may also be possible to make human pluripotent stem cells by using somatic cell nuclear transfer -- the technology that received so much attention with the announcement of the birth of the sheep, Dolly. Although there has been no scientific publication of this to date, presumably any cell from the human body (except the egg or sperm cell) could be fused with an enucleated egg cell and stimulated to return to highly immature, pluripotent and possibly totipotent state.

The Role of the Federal Government

Federal funds were not used in either of the experiments that you will hear about today. First, let me first address Dr. Thomson's work in which cells were derived from embryos created by in vitro fertilization but not used for infertility treatment. This work falls clearly within the Congressional ban on human embryo research. NIH could not, and did not, support Dr. Thomson's recent work developing this cell line.

The same restrictions do not apply to Dr. Gearhart's work, although it may be governed by other laws and regulations. Dr. Gearhart derived his pluripotent stem cells from fetal tissue from terminated pregnancies. The Public Health Service Act authorizes Federal funding of human fetal tissue research and provides safeguards for its conduct. The department may conduct or support research on the transplantation of human fetal tissue for therapeutic purposes if a number of statutory requirements are met. Thus, if Dr. Gearhart's research falls within these boundaries, NIH could have supported his recent work deriving pluripotent stem cells from fetal tissue, as long as he followed these Federal statutes and regulations. For the record, NIH did not, however, support any of this research.

Ethical Issues

I have just described the science and the medical promise of research on the pluripotent stem cell. But the realization of this promise is also dependent on a full and open examination of the social and ethical implications of this work. The fact that these stem cells were produced from embryos and fetal tissue raises a number of ethical concerns including, for example, the need to ensure that stem cell research not encourage the creation of embryos or the termination of pregnancies for research purposes. In strict accordance with the President's 1994 directive, no NIH funds will be used for the creation of human embryos for research purposes. We also will continue to abide by relevant statutes.